The Effect of Memory

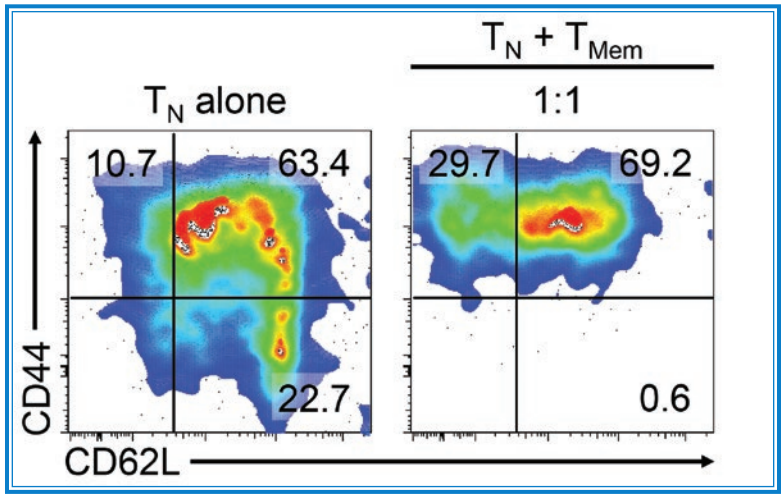
Adoptive cell transfer for cancer therapy may be hindered by memory T cells.

Though still experimental, adoptive cell transfer (ACT) to treat metastatic cancer has seen some dramatic successes (See "Going Home to Kansas," in this issue). In one form of ACT, a patient's own lymphocytes are extracted from their tumor and manipulated to mount a stronger attack against their cancer. The extracted T cells are stimulated with a tumor antigen; the cells that recognize that antigen survive and proliferate, whereupon they are re-injected into the patient.

Extracted cells are typically a mixed population of so-called naïve T cells (those that have not previously encountered antigen) and memory T cells. Once primed, naïve T cells progressively differentiate into memory cells of three varieties: stem cells, central cells, and effector memory cells.

A variety of evidence suggests that having more naïve T cells at the outset promotes a better outcome in ACT. In a recent issue of *Journal of Clinical Investigation*, Christopher Klebanoff, M.D., Staff Clinician in CCR's Experimental Transplantation and Immunology Branch, and Nicholas Restifo, M.D., Senior Investigator, in CCR's Surgery Branch, led a study to ask what impact the inclusion of other T-cell populations may have during ACT.

First, using mouse models, the team found that mixing naïve T cells with memory T cells caused the naïve cells to differentiate at an accelerated pace into effectors, as reflected in key cellular markers, overall gene expression patterns, and physiological responses (e.g., secretion of IFN-γ). Moreover, when reconstituted into tumor-bearing mice, the mixed cell population was less able to reduce that burden. The effect of memory T cells was dependent on the ratio of memory to naïve cells, on antigen priming, and on direct contact between the memory and naïve T cells. The researchers identified FasL, a cell-surface signaling molecule that is normally associated with apoptosis, as the molecular mediator of this precocious differentiation of naïve T cells.



(Figure: C. Klebanoff, CCR)

Naïve T cells extracted from the blood form a distributed population of cells as measured by two key surface markers (CD44 and CD62L). When mixed 1:1 with memory T cells, they differentiate more rapidly. T_N = naïve T cell, T_{Mem} = memory T cell.

Finally, the team wanted to establish the relevance of this precocious differentiation to ACT in patients. They found the ratio of memory to naïve T cells in humans is greater than one, and may be as high as 18 in cancer patients, likely due to chemotherapies that are administered prior to ACT. By separating, labeling, and recombining these populations, they were able to repeat *in vitro* the precocious differentiation of naïve T cells observed in mouse cells.

"The direct interaction of T-cell populations to influence their collective behavior in response to priming is reminiscent of the ways in which single-celled organisms such as bacteria exhibit quorum sensing responses to optimize their behavior as a population," said Klebanoff. What may be effective for the normal immune response, however, is likely a problem for ACT. These findings have led directly to the initiation of a clinical trial to selectively enrich the population of naïve T cells before ACT.

To learn more about Dr. Klebanoff's research, please visit his CCR website at https://ccr.cancer.gov/experimental-transplantation-and-immunology-branch/christopher-a-klebanoff

To learn more about Dr. Restifo's research, please visit his CCR website at https://ccr.cancer.gov/surgery-branch/nicholas-p-restifo.